

Hypertrophic cardiomyopathy: an important cause of sudden death

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SUMMARY Retrospective analysis was performed to assess the natural history in relation to clinical and haemodynamic features in 37 patients in whom hypertrophic cardiomyopathy had been diagnosed in childhood. At diagnosis they were aged 1 to 14 years (mean 9 years). Eighteen presented with chest pain and either dyspnoea or symptoms of impaired consciousness or both; 19 were asymptomatic and were referred for evaluation of abnormalities detected during physical examination. During a mean follow up of nine years, 18 patients died, a cumulative annual medical mortality of 4.8%. Five patients experienced severe dyspnoea or chest pain: two of these had progressive dyspnoea and died in cardiac failure, and three died after myectomy. The 19 survivors were compared with the 11 sudden deaths. Eleven of the survivors and five of the sudden deaths were asymptomatic. Of 18 clinical, electrocardiographic, and haemodynamic features only syncope and electrocardiographic evidence of right ventricular hypertrophy were associated with sudden death. In children with hypertrophic cardiomyopathy sudden death was common and was not well predicted by clinical, electrocardiographic, or haemodynamic findings. Hypertrophic cardiomyopathy indicates a poor prognosis even if symptoms are absent or mild.

Hypertrophic cardiomyopathy is a familial heart muscle disorder which may become clinically manifest at any age.¹⁻⁴ In adults the natural history is characterised by the slow progression of symptoms and by the occurrence of sudden death.^{5,6} When the diagnosis of hypertrophic cardiomyopathy is made in childhood, those patients who present with or who subsequently develop cardiac failure have a poor prognosis as do affected relatives of probands who have died suddenly.⁵⁻⁷ Most children, however, in whom hypertrophic cardiomyopathy is recognised, present with minor or paroxysmal symptoms or are detected because of abnormalities found on routine medical examination.⁵ Their prognosis is uncertain. The purpose of this study was to determine the natural history of these patients in relation to clinical and haemodynamic features.

Study patients

Between 1962 and 1980 the diagnosis of hypertrophic cardiomyopathy was made in 54 children aged less than 14 years who were subsequently followed up at the Hammersmith Hospital. In 17 the diagnosis was made during family screening of probands with hypertrophic cardiomyopathy. These

patients, however, were excluded from the study because they were usually assessed after the sudden death of a sibling or parent. Patients with a bad family history are recognised to be at particular risk of dying suddenly and have previously been well characterised.⁵⁻⁷ Eighteen of the remaining 37 patients presented with symptoms of chest pain, dyspnoea, or impaired consciousness: 19 were asymptomatic and were referred because of abnormalities detected during routine examination. Retrospective analysis was performed on these 37 children to assess their natural history and the prognostic value of clinical, electrocardiographic, and haemodynamic features at the time of diagnosis and at last follow up.

The children were aged 1 to 14 years (mean 9 years) at diagnosis. Twenty two were boys and 15 girls. The follow up was 1 to 21 years (mean 9 years) and all survivors have been seen at follow up examination since July 1982. Twenty three patients were treated with propranolol 20 to 240 mg daily (median 80 mg), 11 received no treatment and three had either digoxin or diuretics, or both. The diagnosis of hypertrophic cardiomyopathy was based on the typical clinical, haemodynamic, and angiographic features.⁸ In 33 patients the diagnosis was estab-

lished by left and right ventricular haemodynamic and angiographic studies. Of the four patients in whom the diagnosis was made without invasive studies, two had clinical or echocardiographic features consistent with hypertrophic cardiomyopathy and were first degree relatives of probands, and two had the typical clinical and M mode echocardiographic features of hypertrophic cardiomyopathy and a left ventricular gradient.⁹ Patients were considered to have a left ventricular gradient if the pressure difference between the body of the left ventricle and the aorta was greater than 20 mm Hg under basal conditions or during provocation (at first with isoprenaline infusion, later with the Valsalva manoeuvre or amyl nitrate). During catheterisation and angiography additional cardiac abnormalities were detected in five patients—one had a small ventricular septal defect, two had moderate to severe mitral regurgitation, and two had mild aortic incompetence.

The electrocardiograms recorded at the time of diagnosis and at last follow up were evaluated for rhythm disturbances, particularly atrial fibrillation; conduction disease including the PR interval, the QT interval corrected for heart rate ($QT_c = QT \sqrt{R-R}$ interval), left axis deviation (mean frontal plane QRS axis -30° to -150°) and bundle branch block; left and right atrial enlargement; and voltage criteria of left and right ventricular hypertrophy.^{10 11}

Analysis of data

The survivors were compared with those patients who died suddenly and those who died in cardiac failure or after myotomy or myectomy. The χ^2 test or, when appropriate, Fisher's exact test were used for qualitative comparison of clinical, electrocardiographic, and haemodynamic features of the survivors and the dead. Cumulative survival rates were derived from life table calculations.¹²

Results

The 37 patients were followed for a mean of 9 years, during which 18 patients (49%) died: 11 (30%) suddenly, two (five per cent) from cardiac failure, three (eight per cent) perioperatively after myotomy or myectomy, one from endocarditis (three per cent), and one from suicide (Figure). Eleven were boys and seven girls. Their age at death was 6 to 23 years (mean 14 years) and their survival was 2 to 13 years (mean 6 years) from the onset of symptoms and 1 to 12 years (mean 6 years) from diagnosis. The age at diagnosis of those who died and survived was identical (1 to 14 years, mean 9 years), however, follow up in the survivors was significantly longer

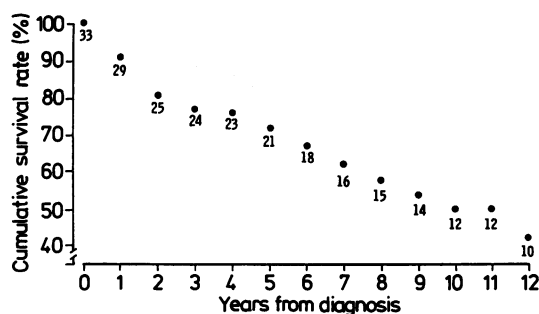


Figure Cumulative survival curve from the year of diagnosis for 33 medically treated patients.

The probability of death = the total number of deaths for the year divided by the adjusted number at risk minus the number of deaths due to other causes. The annual mortality in medically treated patients was 4.8%.

from the onset of symptoms (1 to 21 years, mean 13 years; $P < 0.01$) and from diagnosis (1 to 21 years, mean 12 years; $P < 0.01$).

Nineteen patients were asymptomatic at diagnosis; none of these developed symptoms during a follow up of 2 to 21 years (mean (SD) 10 (7) years), however, four died suddenly. Seven of the 18 patients who presented with symptoms at diagnosis experienced either presyncopal or syncopal episodes or both; 12 had dyspnoea grade 2 and two had dyspnoea grade 3 of the New York Heart Association classification; and eight had exertional chest pain. Seven of the 18 patients died suddenly during a follow up of 1 to 9 years (mean (SD) 5 (3) years). The proportion of patients with chest pain and dyspnoea was similar (Table 1) in those who died suddenly and in the survivors but either presyncope or syncope, or both, were more common in patients who died suddenly ($P < 0.01$).

A clinical summary of those patients who died suddenly is presented in Table 2. One of the 11 had a normal electrocardiogram at diagnosis; in two

Table 1 Clinical, electrocardiographic and haemodynamic findings in 19 survivors and in 11 patients who died suddenly

	Alive No (%)	Sudden death No (%)
Chest pain	3 (16)	3 (27)
Dyspnoea	6 (32)	3 (27)
Syncopal	1 (5)	6 (55)
Left ventricular hypertrophy	14 (74)	8 (73)
Right ventricular hypertrophy	1 (5)	4 (36)
Left ventricular gradient	10 (59)	5 (56)
Right ventricular gradient	7 (41)	5 (56)

* 17 of 19 survivors and 9 of 11 of those who died suddenly had left and right heart catheterisation.

Table 2 Clinical summary of patients who died suddenly

Case No	At diagnosis		Symptoms	ECG	Haemodynamics (mm Hg)				Symptoms at follow up	Age/events at death	Heart weight
	Age (years)	Family history			LVEDP	LV gradient	RVEDP	RV gradient			
1	5	HCM+SD	Asymptomatic	Normal	—	—	—	—	None	16—walking	490 g
2	6	None	Asymptomatic	BVH	20	20	4	45	None	9 —	—
3	12	None	Dyspnoea (2); [†] CP; palpitations	RBBB	15	90	7	28	SOBOE; CP; palpitations	20 —	1160 g
4	13	HCM	Presyncope	ST Δ V5-6	18	0	3	0	Presyncope; dyspnoea	15 —	—
5	13	None	Dyspnoea (2); CP	—	—	—	—	—	—	—	—
6	7	None	Asymptomatic	BVH	15	70	5	20	None	15—sedentary	—
7	3	HCM+SD	Syncope	LVH	14	0	5	0	None	7—walking	No necropsy
8	8	None	Asymptomatic	RAD; RVH	10	45	5	7	None	9 —	No necropsy
9	7	None	Syncope	BVH	12	75	3	0	None	13 —	—
			Recurrent syncope; dyspnoea (2)	Minor ST Δ V4-6	22	0	14	0	Recurrent syncope; dyspnoea (2)	8—walking	—
10	13	HCM	Palpitations	LVH; T ↓	—	—	—	—	None	20—during intercourse	900 g
11	14	HCM	Presyncope; CP	LAD; LVH+T ↓	18	55	8	25	Presyncope; CP	23—talking	680 g

LVEDP=left ventricular end diastolic pressure; RVEDP=right ventricular end diastolic pressure; LVH=left ventricular hypertrophy; BVH=biventricular hypertrophy; LVH+T ↓=left ventricular hypertrophy with T wave inversion; HCM=hypertrophic cardiomyopathy; SD=sudden death; palpitations=palpitations; CP=chest pain; atyp CP=atypical chest pain; RBBB=right bundle branch block; ST Δ=ST change; LAD=left axis deviation; RAD=right axis deviation; SOBOE=shortness of breath on exertion.

[†]Patient 6 was resuscitated from ventricular fibrillation at age 1 year, but subsequently (aged 7) adequate cardiac output could not be restored after D/C conversion of the same arrhythmia.

[‡]Figures in parentheses after dyspnoea are grades according to the New York Heart Association classification.

Table 3 Clinical summary of patients who died in cardiac failure or perioperatively after myotomy or myectomy

Case No	At diagnosis		Symptoms	ECG	Haemodynamics (mm Hg)				Symptoms at last follow up	Age/events at death
	Age (years)	Family history			LVEDP	LV gradient	RVEDP	RV gradient		
1*	8	None	Dyspnoea (2) [†]	LVH; ST Δ	20	50	10	35	Dyspnoea (3); palpitations; presyncope; syncope	20—congestive cardiac failure
2*	1	HCM	Dyspnoea (4)	AF; LVH; ST Δ	10	140	7	0	Dyspnoea (4); CP; palpitations	6—perioperatively
3	12	None	Dyspnoea (3)	LVH; ST Δ	22	51	10	0	Dyspnoea (3); palpitations	13—perioperatively
4	11	HCM	Dyspnoea (2); CP	LVH; ST Δ	12	80	8	0	Dyspnoea (2); CP	12—perioperatively
5	8	None	Dyspnoea (3)	RBBB	24	0	15	0	Severe BVF	8—congestive cardiac failure

LVEDP=left ventricular end diastolic pressure; RVEDP=right ventricular end diastolic pressure; HCM=hypertrophic cardiomyopathy; SD=sudden death; palpitations=palpitations; CP=chest pain; LVH=left ventricular hypertrophy; AF=atrial fibrillation; ST Δ=ST change; RBBB=right bundle branch block; BVF=biventricular failure.

[†]Necropsy examination was performed in cases 1 and 2 and their heart weights were 405 and 335 g respectively.

[‡]Figures in parentheses after dyspnoea are grades according to the New York Heart Association classification.

others the only abnormalities detected were minor repolarisation changes in leads V4–V6. Another had voltage criteria of right ventricular hypertrophy with a mean frontal plane voltage of 110° at diagnosis. During follow up the axis shifted leftward ($+30^\circ$) and there was progressive increase of voltage in lead AVL and SV1+RV5 and 70 mV respectively. The remainder all had electrocardiographic evidence of left ventricular hypertrophy and three of these also fulfilled voltage criteria for right ventricular hypertrophy. Left ventricular hypertrophy was equally common (73%) and the voltage in SV1+RV5 was similar among survivors (mean (SD) 44 (25) mV) and those who died suddenly (45 (24) mV), however, only one of the survivors had electrocardiographic evidence of right ventricular hypertrophy: this finding was associated with sudden death ($P<0.04$). Left ventricular end diastolic pressure was not significantly different in the survivors (5 to 27 mm Hg, mean 14 mm Hg) and in those who died suddenly (10 to 22 mm Hg, mean 16 mm Hg) and the proportion of those with a left ventricular gradient at rest or after provocation was also similar (59 and 56% respectively). Right ventricular end diastolic pressure was 2 to 16 mm Hg (mean 6 mm Hg) in the survivors and 4 to 14 mm Hg (mean 6 mm Hg) in those who died suddenly. Though the proportion of patients with right ventricular gradients was greater in those who died suddenly (56 v 41%), this difference was not significant (Table 1). A similar proportion of survivors and those who died suddenly received propranolol (68 and 73% respectively).

Only three patients had progressive symptomatic limitation of exercise tolerance, however, these and the two patients with severe symptoms at diagnosis all died—two in cardiac failure and three perioperatively after myotomy or myectomy. The clinical features of these five patients are presented in Table 3. They had raised left and right ventricular end diastolic pressures but there was no other electrocardiographic or haemodynamic feature which distinguished them from the survivors.

Discussion

Clinical presentation with hypertrophic cardiomyopathy in childhood was associated with poor prognosis. Approximately half of the patients were dead nine years after diagnosis. This high mortality occurred despite selection criteria which excluded from the study those patients with affected family members who had died suddenly, a group recognised to be at particular risk.^{5–7} This study confirmed that children with hypertrophic cardiomyopathy who have severe or progressive symp-

toms have a grim prognosis.³ More importantly it also showed that those patients with minimal or no functional limitation, who may have been considered to have a benign prognosis also had a poor prognosis with an annual mortality from sudden death of 4.3%. Eleven of the 18 deaths were sudden, and of these only two had severe limitation of exercise tolerance.

Which clinical features identify the child with hypertrophic cardiomyopathy who is at particular risk of sudden death? A history of episodes of impaired consciousness and electrocardiographic evidence of right ventricular hypertrophy were the only clinical, electrocardiographic, or haemodynamic features which distinguished those patients who died suddenly from the survivors. In this study, though episodes of presyncope or syncope were specific (86%), they were not sensitive as approximately half of the children who died suddenly had never experienced symptoms of impaired consciousness. Most patients in this study were evaluated before the availability of good quality echocardiographic recordings, and therefore electrocardiographic criteria were used to assess the presence and magnitude of left and right ventricular hypertrophy. Though electrocardiographic voltage criteria for right ventricular hypertrophy was associated with sudden death, the numbers involved were small and the assessment of right ventricular hypertrophy in the presence of left ventricular hypertrophy is difficult. Prospective echocardiographic confirmation of this finding is warranted. No difference was detected in the incidence or severity of electrocardiographic left ventricular hypertrophy in the survivors and in those who died suddenly. This is consistent with findings in previous studies in which there is a wide spectrum of myocardial hypertrophy both in adults and in children with hypertrophic cardiomyopathy who die suddenly.^{3, 6, 13} Hypertrophy is a non-specific marker for the underlying distribution of the disease. Though unproved it is logical to hypothesise that myocardial cellular disarray and myofibrillary disorganisation may predispose to arrhythmia and a myocardium which is electrically unstable. The findings by Maron *et al* of more noticeable myocardial cellular disarray in young patients compared with adults with hypertrophic cardiomyopathy who have died suddenly is consistent with this interpretation.^{14, 15}

The mechanism of sudden death in hypertrophic cardiomyopathy is unknown, but a propensity either to acute haemodynamic change or to ventricular arrhythmias, or both, is likely to be an important determinant. In adults with hypertrophic cardiomyopathy there is a 2.5% annual mortality from sudden death⁶ and approximately 25% of patients

experience asymptomatic episodes of non-sustained ventricular tachycardia.^{17 18} The detection of ventricular tachycardia during ambulatory electrocardiographic monitoring is a sensitive clinical marker of those patients who are at particular risk. During treatment with conventional anti-arrhythmic agents the annual mortality from sudden death in these patients is approximately eight per cent.^{16 18} The incidence and importance of arrhythmias in children with hypertrophic cardiomyopathy is unknown. Information from small numbers of patients suggests that serious ventricular arrhythmias are less common than in adults and arrhythmias have not been detected in the small number of children who have had electrocardiographic monitoring performed before sudden death (unpublished data).

Can sudden death be prevented in these children? Beta blockers, calcium antagonists, and surgical myectomy are effective in the management of symptoms but their effect on prognosis has not been prospectively evaluated.⁶ The available evidence in adults, however, does not suggest that they will prevent sudden death.⁶ In the largest medical series, 28 of 32 patients who died suddenly were receiving propranolol⁵ (mean dose 220 mg daily). The results from the surgical centre with most experience show an annual mortality from sudden death of approximately two per cent after successful surgical myectomy and, furthermore, an eight per cent perioperative mortality.¹⁹ The only treatment which has shown promise in reducing sudden death is amiodarone.²⁰ In adults with hypertrophic cardiomyopathy and ventricular tachycardia a non-randomised study showed no mortality over three years in 21 patients on amiodarone in comparison with an eight per cent annual mortality in a matched population treated with conventional anti-arrhythmic agents.²¹ These results in adults, however, cannot be extrapolated to children. The cause of sudden death may be different in adults and children, and in addition amiodarone is associated with a high incidence of dose related, unwanted side effects. Thus, before a recommendation for treatment of children can be made, the antecedent mechanism of sudden death must be defined better to provide a rationale for treatment.

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